Charting New Horizons in Education

T-cell mediated immune response

9

Part 1
Immunology

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Cross Presentation

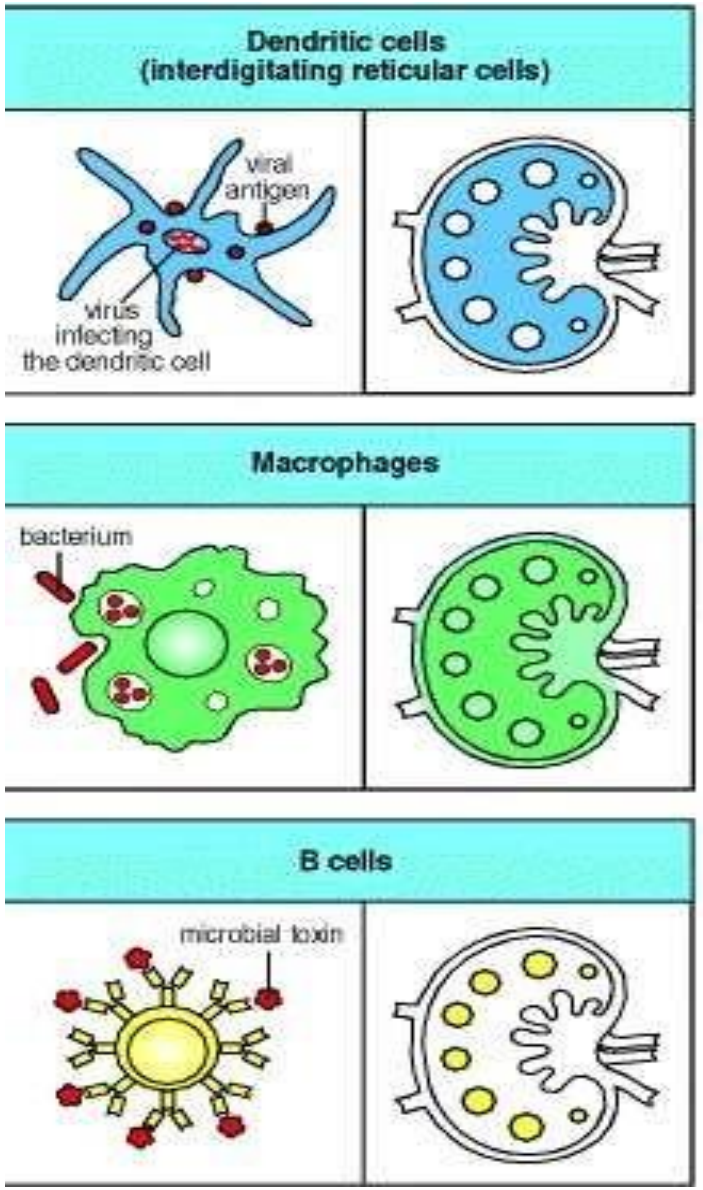
•The **class I MHC pathway of antigen presentation to CD8+ T cells** requires that protein antigens be present in the cytosol of infected presenting cells.

•When a virus infects a specific cell type, it may be taken into **antigen-presenting cells (APCs)** by phagocytosis. However, these APCs are not infected by the virus and therefore do not endogenously synthesize viral antigens. The immune system addresses this challenge through **cross-presentation**.

- In **cross-presentation**, **dendritic cells** ingest infected cells, tumor cells, or proteins expressed by these cells.
- These antigens are initially expressed on **MHC class II molecules**; however, dendritic cells also transfer the protein antigens into the cytosol.
- The antigens are then processed to enter the **class I MHC antigen presentation pathway** for recognition by **CD8+ T cells** and **Th1 cells**.

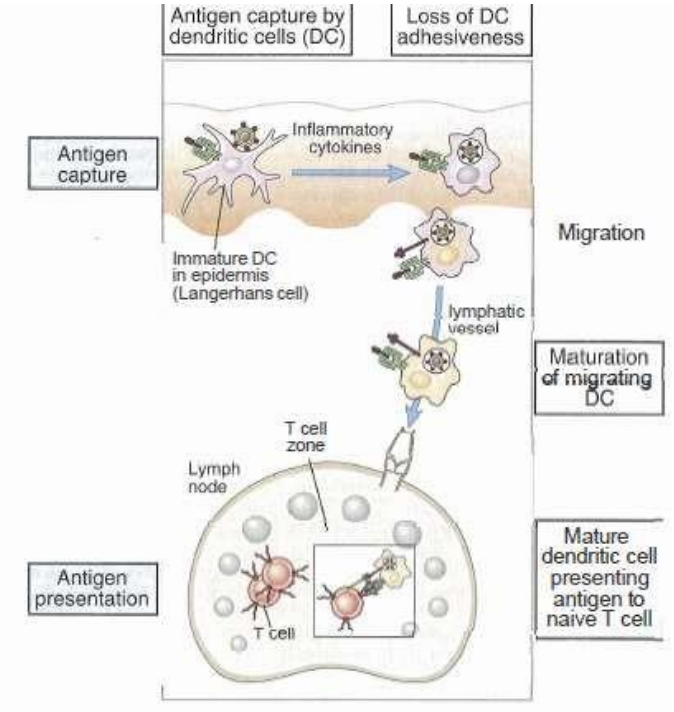
Antigen-Presenting Cells (APCs)

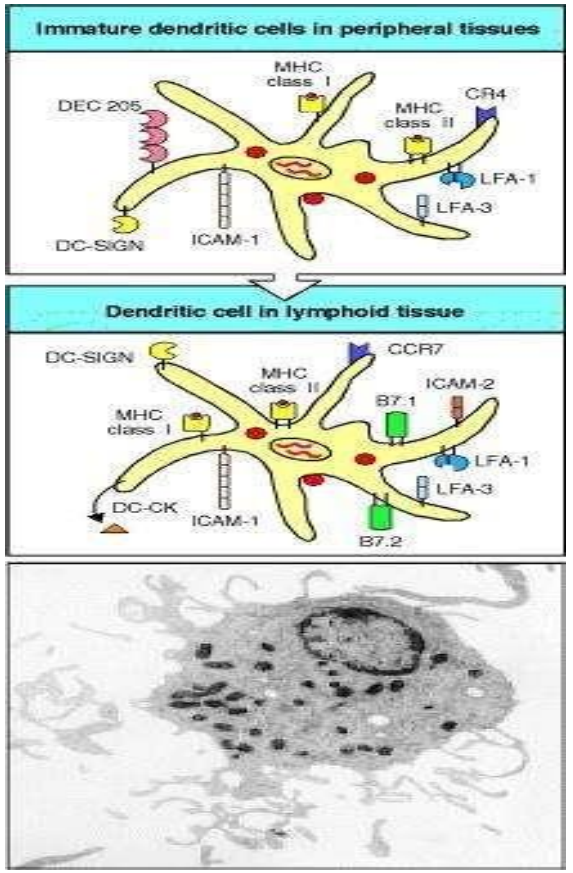
- **APCs** are distributed throughout tissues, blood, and lymph nodes and include **dendritic cells, macrophages, and B cells**.
- **Mature dendritic cells** are the most important activators of naive T cells and can be activated by a wide range of antigens, including viral, bacterial, and allergenic antigens.
- **B cells** bind soluble, intact antigens and present them to **T helper (TH) cells** via **MHC class II molecules**.



Dendritic Cells activation

- **Immature dendritic cells** exist to tissues and sites of infection.
- They express low levels of **MHC class I and II** molecules and **phagocytic receptor PRRs**, but have low levels of adhesion molecules.
- **Internalization** of antigens occurs through:
  - **Binding of antigens** with PRRs.
  - **Macropinocytosis.**
- After engulfing the pathogen, dendritic cells become **mature dendritic cells** and undergo several changes:
  - They **migrate to peripheral lymph nodes (LNs)**.
  - **Lose their phagocytic activity.**
  - **Express increased levels of adhesion molecules, MHC, and co-stimulatory molecules.**
  - Secrete **chemotactic factors** to attract naive T cells to the lymph nodes.





B Cell as APC

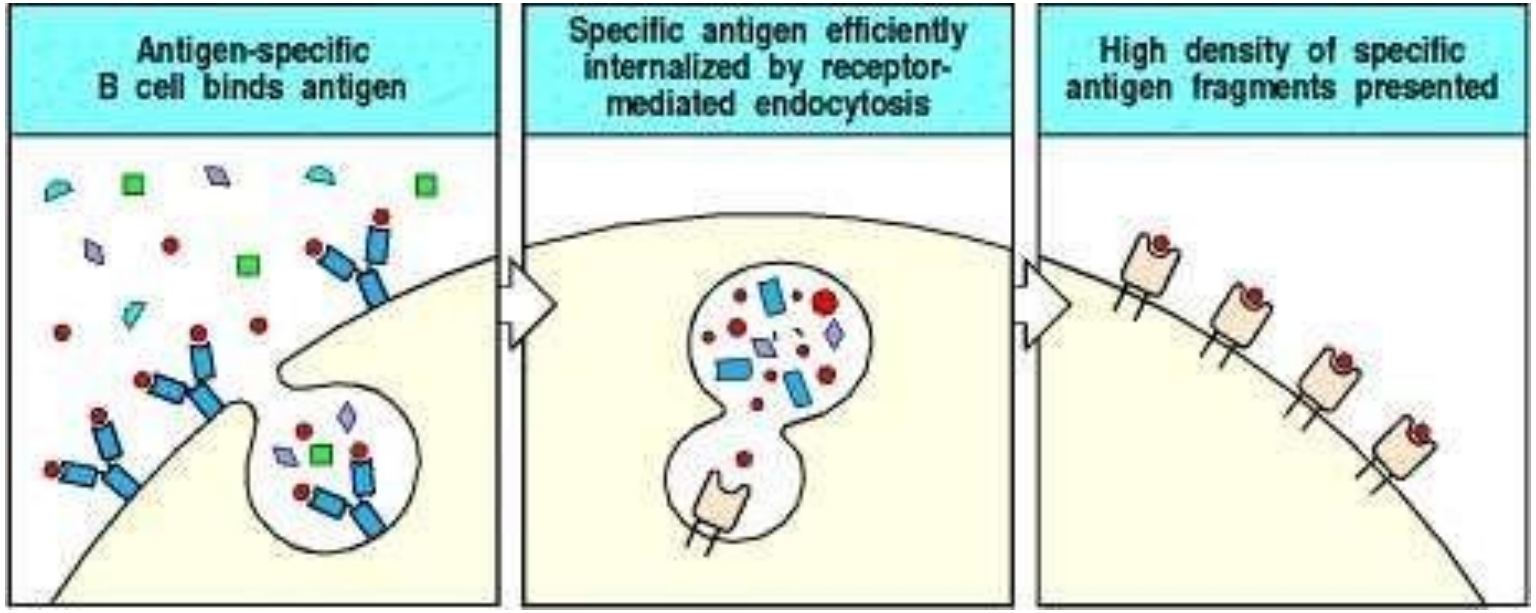
•**Surface immunoglobulins (IgM or IgD)** enable B cells to bind and internalize specific soluble intact antigens with high efficiency.

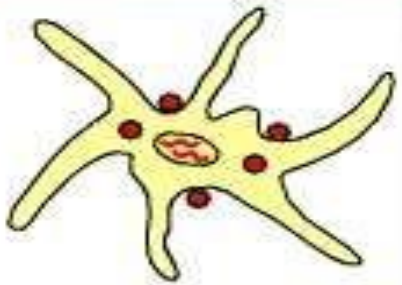
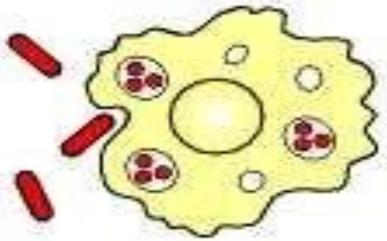
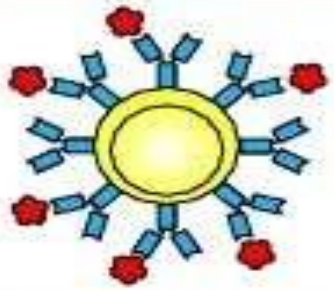
•Once internalized, the antigen is **processed in intracellular vesicles**, where it binds to **MHC class II molecules**.

•These vesicles are then transported to the cell surface, where the **MHC class II**

•**complex** can be recognized by **Th2 cells**.

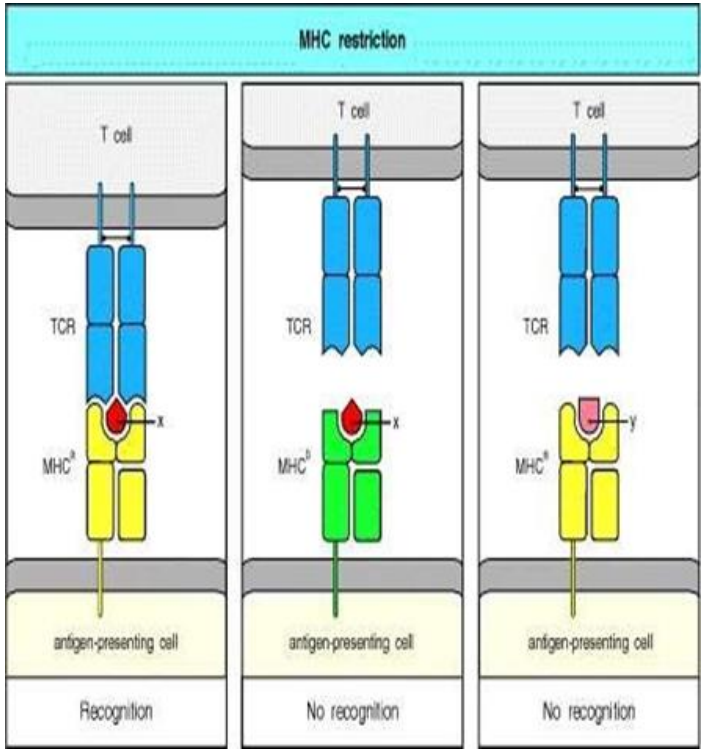
•Due to the high specificity of this process, it is especially effective when antigen concentration is low.

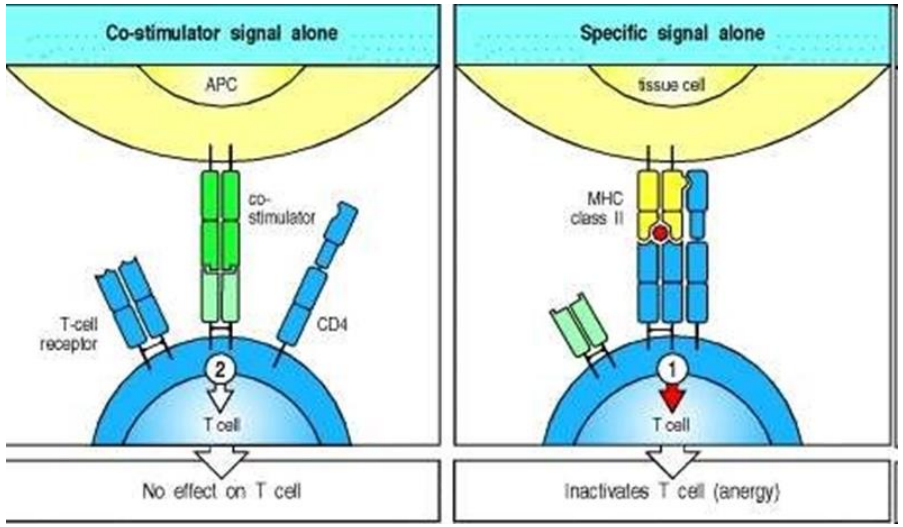


	Dendritic cells	Macrophages	B cells
			
Antigen uptake	+++ Macropinocytosis and phagocytosis by tissue dendritic cells Viral infection	Phagocytosis +++	Antigen-specific receptor (Ig) ++++
MHC expression	Low on tissue dendritic cells High on dendritic cells in lymphoid tissues	Inducible by bacteria and cytokines – to +++	Constitutive Increases on activation +++ to ++++
Co-stimulator delivery	Constitutive by mature, nonphagocytic lymphoid dendritic cells ++++	Inducible – to +++	Inducible – to +++
Antigen presented	Peptides Viral antigens Allergens	Particulate antigens Intracellular and extracellular pathogens	Soluble antigens Toxins Viruses
Location	Lymphoid tissue Connective tissue Epithelia	Lymphoid tissue Connective tissue Body cavities	Lymphoid tissue Peripheral blood

Inappropriate Antigen or MHC

- **CD4** binds to **MHC class II**, while **CD8** binds to **MHC class I**.
- The **T cell receptor (TCR)** binds both the antigen and a part of the MHC molecule.
- When **self-antigens** are presented, **immature dendritic cells (DCs)** and macrophages do not express co-stimulatory molecules, leading to **T cell anergy**.





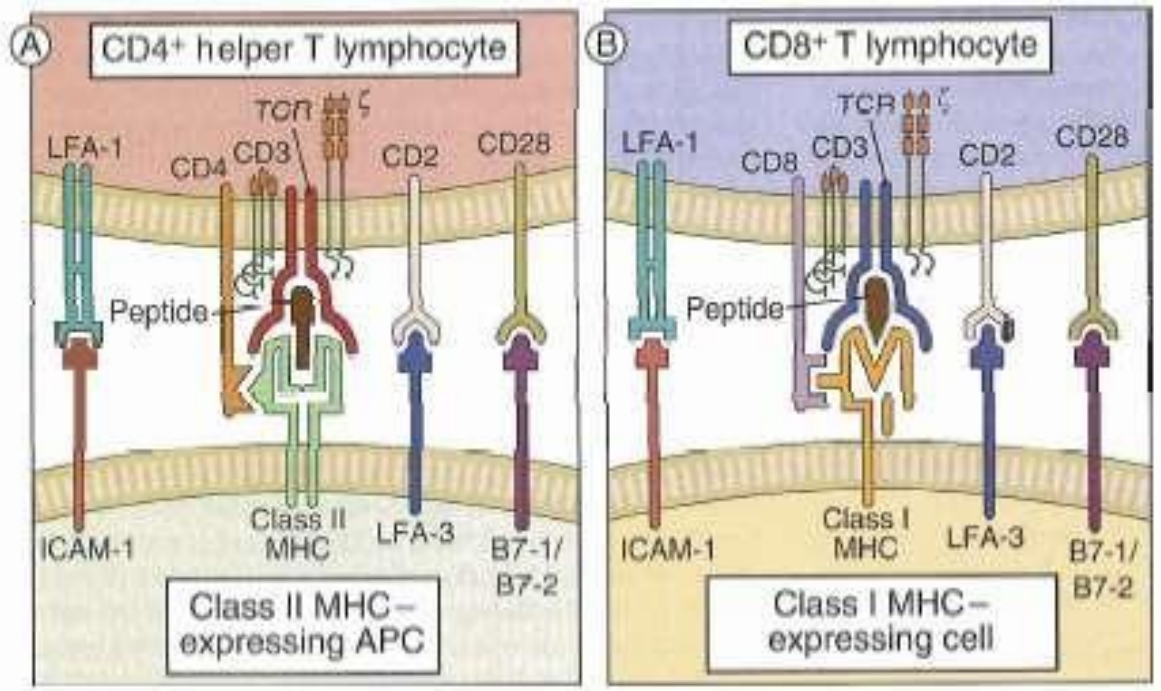
The Immunologic Synapse

•When the **TCR complex** recognizes **MHC-associated peptides** on an antigen-presenting cell (APC), several T cell surface proteins and intracellular signaling molecules are rapidly mobilized to the site of T cell–APC contact.

•This region of physical contact between the T cell and the APC is called an **immunologic synapse** or **supramolecular activation cluster (SMAC)**.

•The **T cell molecules** rapidly mobilized to the center of the synapse include:

- The **TCR complex** (composed of the TCR, CD3, and ζ chains).
- **CD4 or CD8 coreceptors.**
- **Receptors for costimulators** (such as CD28).
- **Enzymes and adaptor proteins** that associate with the cytoplasmic tails of transmembrane receptors



Memory T Cells

•Both **CD4+ and CD8+ memory T cells (CD45RO+)** can be subdivided into two subsets based on their homing properties and functions:

- **Central memory T cells:** These cells express the **chemokine receptor CCR7** and **L-selectin**, homing mainly to **lymph nodes**.
- **Effector memory T cells:** These cells do not express **CCR7** or **L-selectin** and home to **peripheral sites**, especially **mucosal tissues**.

•During a **secondary infection**, memory T cells in peripheral tissues can be directly activated by **pro-inflammatory cytokines** to initiate effector functions outside of the draining lymphoid tissue.

Regulation of T Lymphocyte Responses

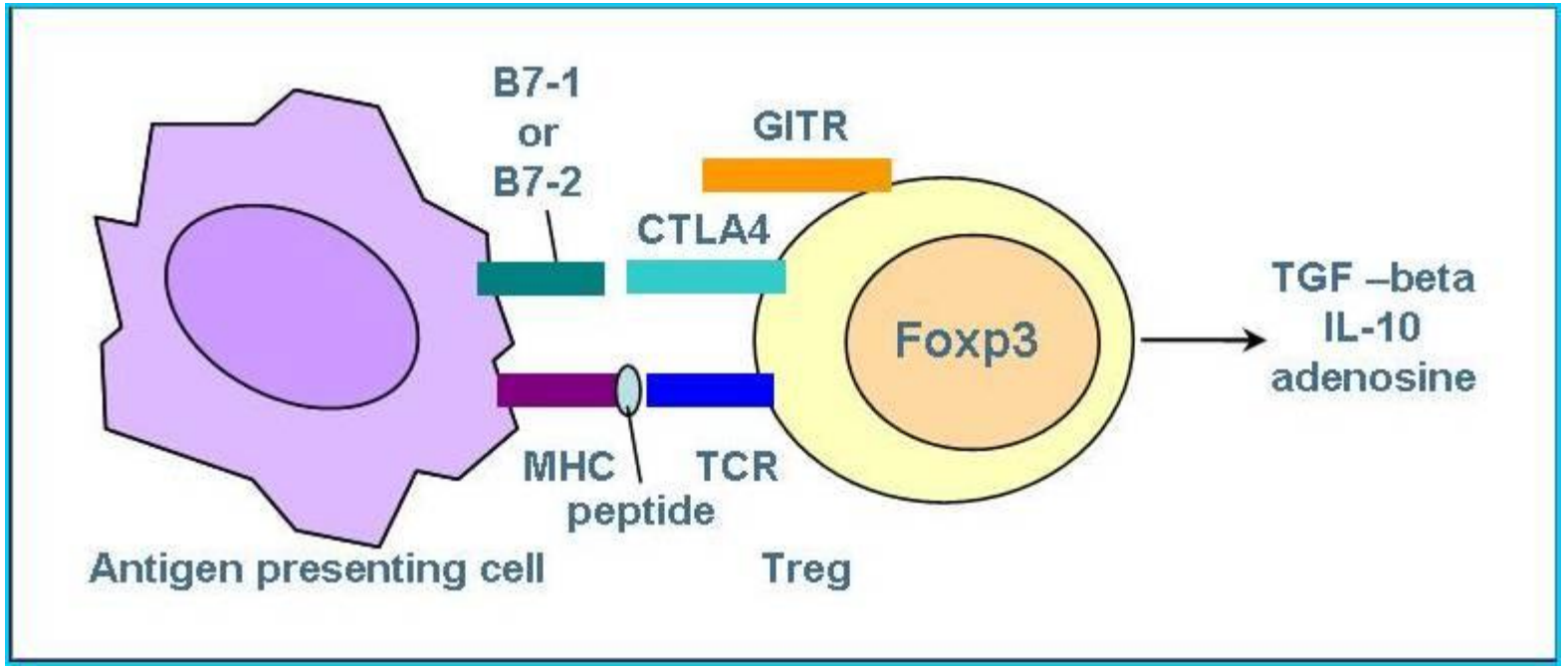
- **Purpose of Regulation:**
  - To prevent **tissue damage** from overstimulation.
  - To prevent **autoimmunity**.
- **Methods of Regulation:**
  - After clearing the antigen, **CTLA-4** is expressed instead of CD28 on T cells. CTLA-4 binds to **B7 on APCs** and inhibits T cell activity.
  - **Persistent activation of T cells** leads to **activation-induced cell death (AICD)** through Fas-FasL surface interactions on natural killer (NK) cells with the target T cell.
  - **Elimination of the antigen** results in passive cell death of T cells.
  - **CD4 regulatory T cells (T regs)** are induced in the presence of **IL-10 and TGF-beta**.
  - **PD-1 on T cells** (Programmed Cell Death 1) recognizes two ligands, **PD-L1** and **PD-L2**:
    - **PD-L1** is expressed on APCs and various other tissue cells.
    - **PD-L2** is mainly expressed on APCs.
    - Engagement of PD-1 by either ligand leads to **inactivation of T cells** or, in rare cases, **conversion to T reg cells**

New T Cell Phenotypes: Regulatory T Cells

T Cell Phenotypes: Regulatory T Cells

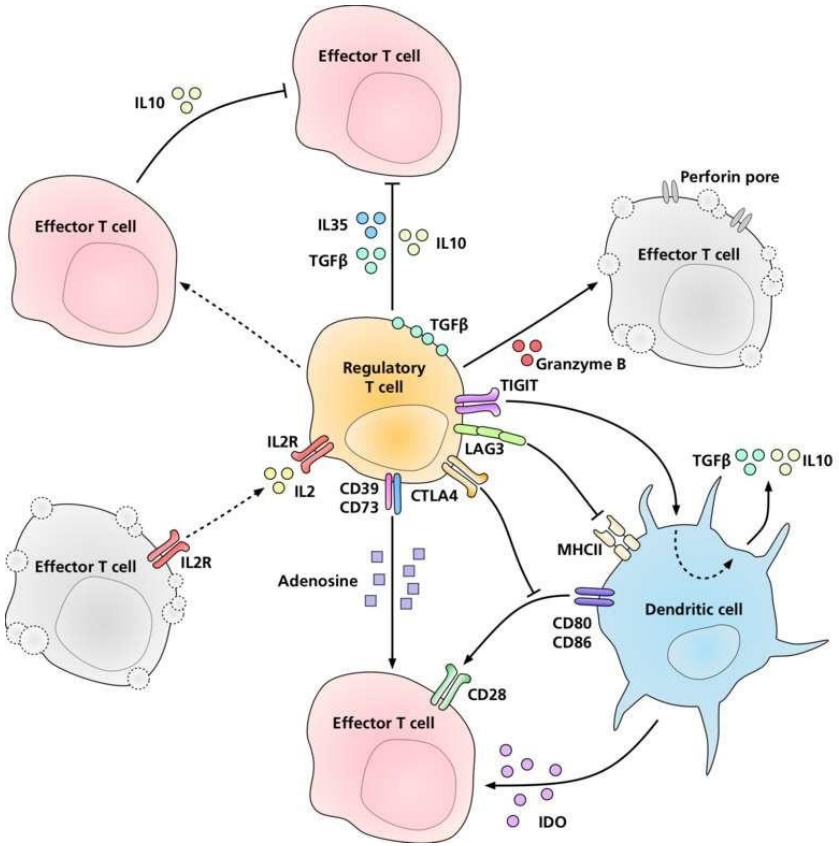
•Subset of CD4 T cells

- **Naturally occurring** regulatory T cells:
  - Positive for **FoxP3**, **CD25**, and **CD4** markers.
- **Induced regulatory T cells:**
  - Generated in the presence of **IL-10** and **TGF-β**.



T Regulatory Cells (T reg)

- **Generation of T reg cells:**
  - Regulatory T cells are generated mainly by **self-antigen recognition in the thymus** (**central** tolerance).
  - They are also generated by recognition of both **self** & **foreign antigens** in **peripheral lymphoid organs** (**peripheral** tolerance).
  - They are differentiated from **CD4+ T cells**.
  - The generation of some T reg cells requires the cytokines **TGF-β** & **IL-2**.
- **Functions of T reg cells:**
  - **Production of immunosuppressive cytokines** such as **IL-10** & **TGF-β**.
  - **Consumption of IL-2:** Due to the high expression of the **IL-2 receptor**, T reg cells may absorb IL-2, depriving other cell populations of this growth factor. This results in reduced proliferation and differentiation of other **IL-2–dependent cells**.
  - **Reduced ability of APCs** to stimulate T cells. One proposed mechanism is the binding of **CTLA-4** on regulatory cells to **B7 molecules** on APCs.
  - **Secretion of granzyme B**: T reg cells secrete **granzyme B**, which acts on activated T cells



T reg Cytokines

- **TGF-β**:
  - Inhibits **T cells** and **macrophages**.
- **Interleukin-10 (IL-10)**:
  - IL-10 is an inhibitor of activated **macrophages**, **dendritic cells**, **TH1 cells**, and **CD8 cells**.
  - IL-10 inhibits the production of **IL-12** by activated dendritic cells and macrophages, which in turn **inhibits TH1** and **CD8 cell** activation.
  - IL-10 also inhibits the expression of **costimulatory molecules** and **class II MHC** molecules.

Privileged Sites

•Immune responses do not normally occur in these sites, such as:

- **Anterior chamber of the eye**
- **Testes**

•This lack of immune response is due to the presence of high levels of **inhibitory proteins**, including:

- **IL-10**
- **TGF-β**
- **Migration inhibition factor**

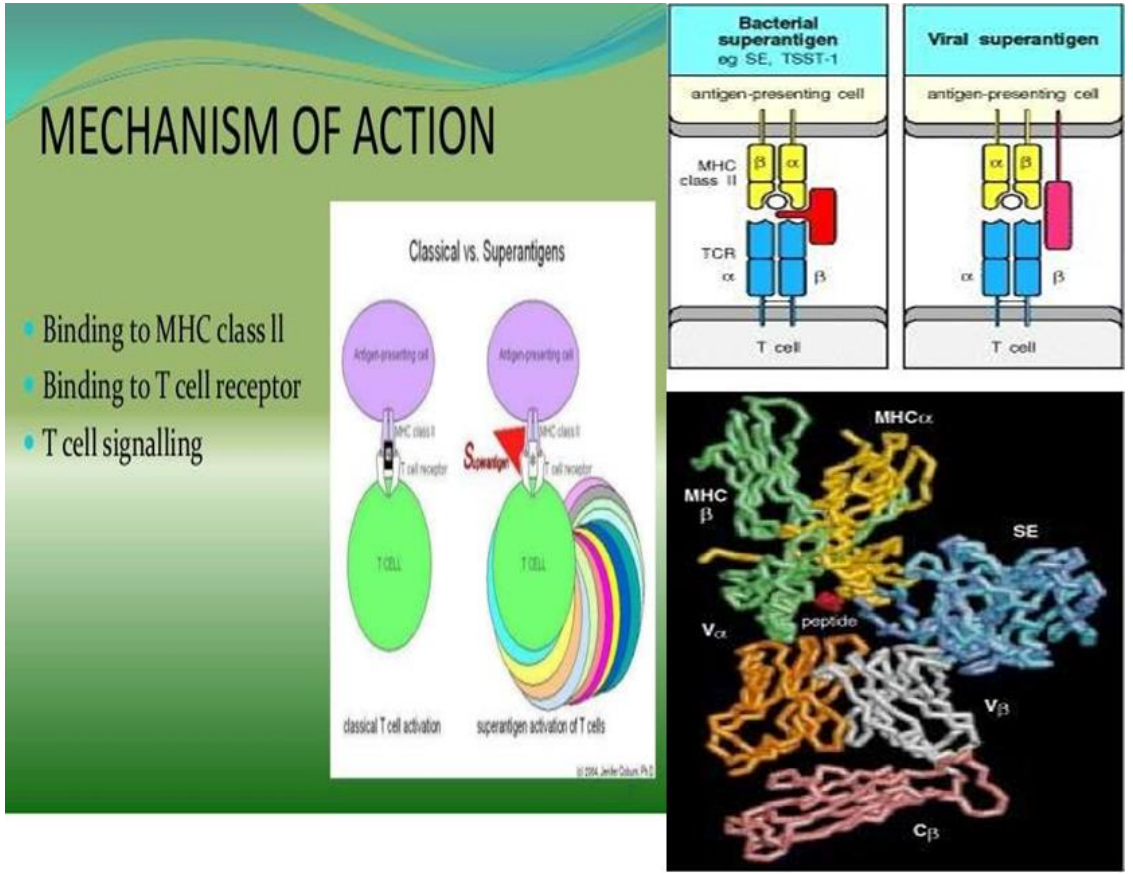
•Additionally, there is **expression of FasL** on the cells in these sites, which helps prevent immune activation.

Inappropriate T Cell Activation

- **T Cell Stimulation by Super Antigens:**
  - **Super antigens** are a class of antigens that cause **non-specific activation** of T cells, leading to massive **cytokine release** from macrophages.
- **Causes:**
  - Super antigens include **exoproteins**, such as:
    - **Toxic shock syndrome toxin-1 (TSST-1)**
    - **Staphylococcal enterotoxins**
    - **Exfoliative toxins (ETA and ETB)**
    - **Leukocidin**
    - **Exotoxins A** from **Streptococcus pyogenes**, which leads to **toxic shock-like syndrome**.
    - Other pathogens include **EBV** and **HIV**.

Inappropriate T Cell Activation

- **Pathology:**
  - Super antigens **bind inappropriately** to the outer part of the **Vß domain** of the TCR and to the outer part of **MHC class II**, causing activation of a massive number of T cells and a huge amount of **cytokines**.
  - The frequency of T cells with antigen-specific **Vß domains** is higher than those with both antigen-specific **Vα** and **Vß TCRs** (10% vs. 0.01%).
- **Immunological Effects:**
  - **Increased levels of IL-1**, **TNF-alpha**, and **IL-2** due to enhanced macrophage activation by T cells.
  - This results in symptoms such as **fever**, massive **vascular leakage**, and **toxic shock syndrome (TSS)**.



Immunoglobulin Superfamily

- The immunoglobulin superfamily includes:
  - **Antigen receptors of T and B cells**
  - **CD3**
  - **Co-receptors CD4** and **CD8**
  - Most **Fc receptors**
  - **CD28** and **B7 adhesion molecules**
  - **Cytokine receptors**
  - **MHC molecules**

«Wherever the art of medicine is loved,
there is also a love of humanity.»

- Hippocrates-

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